compared with conventional techniques such as development of complex products with high accuracy because of the complete digital control, personalization of medication that improves patient compliance, cost-effective and less time consuming, and on-demand manufacturing in case of emergencies. Currently, work is being done to merge 3D printing technology with nanotechnology. This is an emerging field and still a lot of research is required in this area. This technique is limited only to pharmaceutical manufacturing but has found wide applications even in tissue engineering [6, 7, 63].

## 8. ULTRA-LONG ACTING FORMULATIONS

Currently, the most promising gastro-retentive systems are all expandable or swellable systems. Also, all the marketed oral formulations have a gastric retention time of less than 24 h. In the 1980s, unfolding systems such as the tetrahedron were found to have certain advantages when compared with the swelling systems. These systems used elastomeric and biocompatible polymers. The system resided in the stomach after multiple meals. However, it did not cross the 24 h mark in the clinic.

The recent work in the field of unfolding gastro-retentive systems includes polygons, rings, and stellates. Among these, stellates: a star-shaped conformation is more preferred because it can fold easily into the shape of a hard capsule with less stress concentration and deformation. It also ensures more efficient capsule packing [18]. The stellate is composed of modular components, each designed to perform certain functions. It consists of three modular components; a central "core" of elastomer, "arms" loaded with memantine, projecting from the core, and disintegrating matix layers that join the arms and the core. The stellate is folded to fit it in a sized 00EL capsule for oral use. When the capsule dissolves in the stomach, the stellate unfolds and does not pass through the pylorus because of the size of the open configuration. The six arms of the stellate contain the drug and control its release. Disintegrating matrices gradually weaken and cause detachment of the arms from the core after 7 days of gastric retention. This ensures safe passage into the lower GIT from the stomach. The stellate moves freely within the stomach, because it does not depend on any of the conventional mechanisms such as floating and mucoadhesion. Also, it does not affect the normal activity of the stomach. The drug-loaded arms achieve a drug release, that is near linear for 7 days, thus resisting dose dumping [20].

Degludec, a basal insulin analog is the most recent ultra-long acting drug. After its subcutaneous injection, the soluble multihexamers are converted into monomers that are absorbed slowly and continuously [64]. A recent study in type 1 and 2 diabetes mellitus patients showed that degludec exhibited glycemic control at par with detemir or insulin glargine. It also had a better safety profile.

Kovarova and coworkers suggested an ultra-long acting system for HIV prevention and treatment that can deliver drug for 9 months and can be removed safely, thereafter, to halt the drug delivery. It was observed that a single subcutaneous dose of dolutegavir delivered the drug in humanized BLT mice and nonhuman primates effectively. It protected the BLT mice from multiple dose effects of vaginal HIV [65].

Bellinger and colleagues developed an ultra-long acting oral capsule for ivermectin, an antimalarial drug in the stellate form. It was found that the system delivered ivermectin for 14 days in the swine model. This system demonstrated increased efficacy of drug administration and had the potential to be used in malaria and other diseases that require treatment adherence [19].

Thus, the ultra-long acting systems deliver drugs more effectively, efficiently, and consistently with decreased dosing frequency. However, many challenges need to be resolved in the commercialization and development of ultra-long acting systems. Clinical experience and careful engineering is required to address this problem to advance and refine our understanding of these systems [20].

## 9. PATENTED TECHNOLOGIES

A large number of pioneering controlled release technologies find their origin from patents [66]. A few of them are discussed here.

OROS was trademarked by Alza Corporation in 1982, with 20 products. Johnson and Johnson later acquired Alza Corporation. It used osmotic pressure to release the drug from the controlled-release system. A significant advantage of this technology is improved patient compliance because of the reduced dosing frequency. In a single compartment OROS, the osmotic agent and the drug are present in a single compartment that forms the core. The compartment is surrounded by a semipermeable membrane that allows the water to reach the core by osmosis. Thus, the core components dissolve in water and the drug is released. In the multiple compartment OROS, drug is separated from the osmotic agent by a flexible film. Because of the increase in pressure of the osmotic compartment, the drug